

EXHIBIT E

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Digestive System Cancer Among Persons Subjected to Occupational Inhalation of Asbestos Particles: A Literature Review with Emphasis on Dose Response

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Human data show a dose-response relationship between industrial exposure to asbestos and later development of cancer of the bronchus and lung and of cancer of the digestive tract. The data do not provide much evidence for a threshold or for the existence of a clearly "safe" level of exposure. Good dose-response data, with quantitative estimates of dose are uncommon; however, in all the literature reviewed only one paper did not support the conclusion that increased exposure to inhaled asbestos particles leads to increased digestive system cancer.

There are no direct epidemiologic data on the possible carcinogenic affects of ingested asbestos. There are some data relating inhaled asbestos to the subsequent development of digestive tract cancer. Since there is evidence that some portion of inhaled asbestos eventually enters the digestive tract, relationships shown between inhaled asbestos and digestive tract cancer should have some meaning for establishing (or denying) a dose response relationship between ingested asbestos and cancer.

This paper follows this plan to investigate this relationship: review of dose-response relationships between inhaled asbestos and bronchiogenic cancers with emphasis on establishing possible "threshold" or "safe" levels; review of dose-response relationships between inhaled asbestos and digestive system cancers with attempts to determine if the dose-response relationship (if any) is similar to the dose-response relationship for bronchiogenic cancer and inhaled asbestos; review of literature which does not give clear quantitative dose data, but which does address the problems of

digestive system cancers and exposure to asbestos through inhalation.

As a result of this review, the data I have examined suggests to me that there is an increase of digestive tract cancer associated with inhaled asbestos; the proportionality factor for converting inhaled dose to ingested dose to produce digestive cancer with rates at the same level as bronchiogenic cancer ranges from 1/20 to 1/1; for both bronchiogenic cancer and gastric cancer, the data do not provide strong evidence for a threshold, or for the existence of a clear "safe" level of exposure.

The major quantitative dose-response data, with dose given in units of millions of particles per cubic foot-years (mppcf-years), have been given in papers by McDonald (McGill University, Montreal, Canada) and Enterline (University of Pittsburgh, Pittsburgh, Pennsylvania). There are other papers which give dose in semiquantitative terms, and these are considered later.

Figure 1 plots the data given by McDonald (1) and Enterline (2, 3) for cancer of the bronchus and lung. The McDonald data are plotted at the median of the "dust index" (mppcf-years) classes except for his open-ended class of 800 mppcf-years and more, which is plotted at 1130 mppcf-years (which would be the median if the

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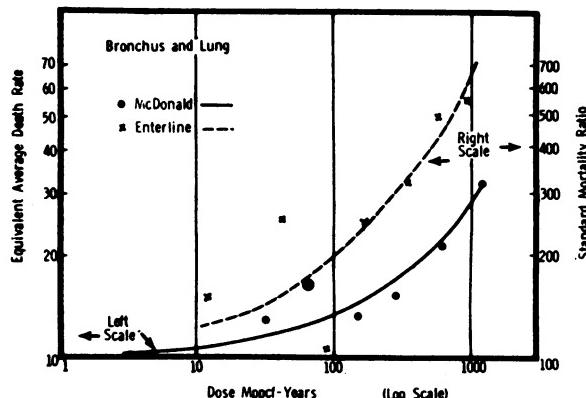


FIGURE 1.

class interval were 800–1600). McDonald's response measure is the "equivalent average death rates," and is given on the left scale. Enterline's measure of response is the standard mortality ratio (SMR), and this is given as the right scale. Enterline gives average dose for each exposure class and the response data are plotted against average dose.

There is one serious inversion in Enterline's data (dose = 25.0–62.4, SMR = 258.1; dose = 62.5–124.9, SMR = 108.7) which apparently led him to combine his three lowest dose groups into one with dose 0–125, avg. 62.9; SMR 166.7. This is shown on Figure 1 as an x enclosed in a circle. The two curves on Figure 1 are fitted by eye and are not an attempt at a mathematical fit. The Enterline data have a steeper dose-response relationship than the McDonald data but this could easily be an artifact, for there are many ways in which the two sets of data are not strictly comparable. First, Enterline considers the experience only of retired workers. The nature of the work experience was quite different, Enterline's being of manufacturing and mill workers, and McDonald's being mine workers. The response scales are also different. There is no formal way to equate SMR to equivalent average death rate, and to make them strictly proportional on a 10:1 scale, as I have done is certainly wrong. The same data are shown on Figure 2 with the scales adjusted to a 20:1 proportionality. With this proportionality the two sets of data appear to be fit by the same line.

I see little evidence in these data for a threshold. One might perhaps fit a line to the Enterline data that crosses the SMR 100 line at

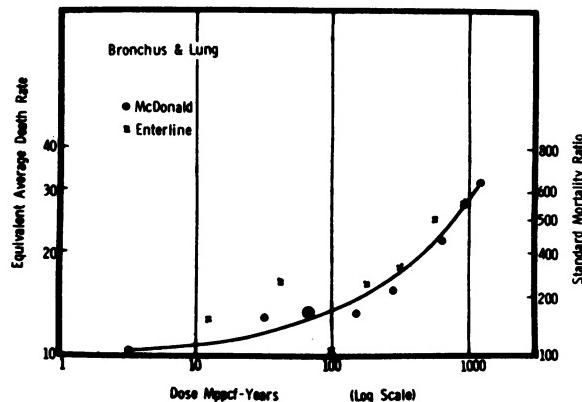


FIGURE 2.

about 30 mpccf-years, but that leaves a SMR of 153.8 for his lowest dose group as an "outlier." With the McDonald data threshold is not directly measurable since he uses the measure equivalent average death rate, to which a "normal" (unexposed population) rate cannot be directly appended.

McDonald says (for lung cancer) "...the excess was virtually confined to persons with a dust index above 200 mpccf-years." I find it hard to talk about "excess" from McDonald's data since he gives no "expected" numbers for each group and hence I have nothing to measure an "excess" from.

Enterline (3) remarks "there appeared to be no direct relationship between dust exposure and respiratory cancer below 125 mpccf-years. Important increments in respiratory cancer mortality apparently occurred somewhere between 100 and 200 mpccf-years." The data Enterline gives are summarized.

Two things are worth noting. First, there is no dose group in the Enterline data in which the SMR is below 100 (100 = "normal"). Second, the

Table 1.

Dose, mpccf-years (avg. in parentheses)	^a Standardized mortality ratio	95% confidence limits on SMR
<25	(11.1)	153.8
25-62.4	(44.4)	258.1
62.5-124.9	(80.1)	108.7
125-249.9	(181.0)	250.0
250-400 (?)	(351.0)	326.9
500-749	(606.1)	500.0
>750	(960.2)	555.6

^a My computation, following Haenszel et al. (4)

95% confidence limits on the SMR's include 100 for two of the three dose groups below 125 mppcf-years. That is, for one of the dose groups (25–62.4) there is a statistically significant excess lung cancer mortality. For the other two, mortality is above expectation but not significantly. Enterline does not define what he calls "important increments" in respiratory cancer mortality but statistically significant excesses did occur at low doses. Sometimes trivial differences are statistically significant because they are based on large numbers. This is not the case here. The number of men in each dose group ranged from 56 to 328. The low dose groups are shown in Table 2.

Table 2.

Dose	Number
25	75
25–62.4	181
62.5–124.9	277

Having satisfied ourselves that there are dose-response data relating asbestos inhalation and respiratory cancer, and that the possibility of no threshold is consistent with the data, it becomes worthwhile to review the same sources with respect to digestive tract cancer. Figure 3 presents the McDonald–Enterline data on the same scales as Figure 2, i.e., EADR ~ SMR/20.

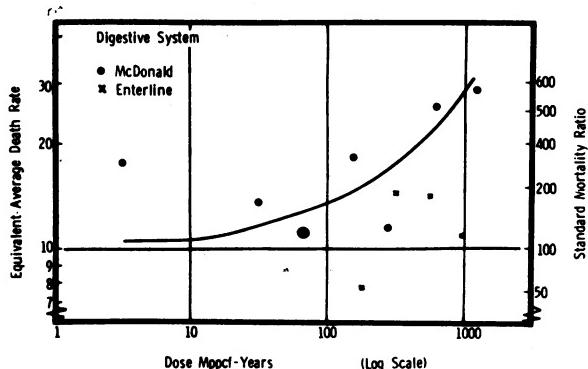


FIGURE 3.

I have drawn the identical dose-response curve on this figure as I did on Figure 2. It looks as if it might possibly fit the McDonald data although it looks both too low at the lower doses, and too steep at the higher doses. But it certainly does not fit the Enterline data. Only one "response" point lies below a SMR of 100.

There are several inversions in the data — both McDonald's and Enterline's have two. If

several of the dose groups were combined leaving four dose groups for McDonald (instead of six) and three for Enterline (instead of five), we would have Figure 4. The curve that fit in Figure 2 and Figure 3 obviously no longer fits (it is drawn in as a "ghost" on Figure 4). The response levels are clearly different for McDonald's miners and Enterline's mill workers. Both show a dose-response relationship which leads me to conclude that there is increased risk of digestive system cancer following the inhalation of asbestos. Because of the differences in the reported results from the two studies anything said about threshold levels for digestive system cancer would be speculative.

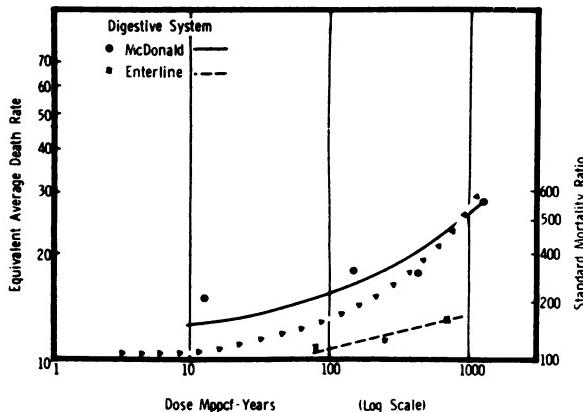


FIGURE 4.

For the dose-response curve from the Enterline digestive system data to coincide with the dose-response curve for the respiratory system cancers, there would have to be a roughly 20-fold dilution of the dose. No such dilution is necessary for the McDonald data. The differences between Enterline and McDonald may possibly be due to: (1) the nature of the populations observed (McDonald, active miners; Enterline, retired mill workers; (2) the relationship between McDonald's response measure (average equivalent death rate) and Enterline's measure (standard mortality ratio) and the possibility of error in the 1:20 proportionality that I have imposed, as a result of looking at the lung cancer data; (3) differences in age-specific incidence for different forms of cancer in populations with different age structures; (4) possible differential effect of smoking on lung cancer (multiplicative) compared to digestive system cancer (possibly additive), no

smoking data given; (5) possible difference in relationship between particles and fibers in different industrial exposures (e.g., in asbestos-cement pipe manufacture $p/f \sim 1.6$; in textile mills $p/f \sim 6.0$); (6) different responses to different forms of asbestos.

Other confounding factors, such as the nature of the exposure (intermittent vs. continuous), which will be discussed later, could also contribute to the differences.

There are several other papers in which partial dose-response data are given. With one exception, all of these support the conclusion that increased exposure to inhaled asbestos particles leads to increased digestive system cancer.

In the study of Mancuso and El-Attar (5) exposure is given in years of employment. A comparison is made with an industrial (employed) control. The expected number of deaths is computed using the industrial control population and SMR computed from observed deaths/expected deaths. For the digestive system 12 cancer deaths were observed compared to 4.37 expected (SMR = 274.6 95% confidence limits 142–481). For the respiratory system SMR = 815.8, 95% confidence limits, 511–1230. The bronchus and lung data show no threshold. The digestive system data are consistent with a threshold of about one year's exposure. The workers reported on in this study were "...engaged in the manufacture of asbestos products."

Elmes and Simpson (6) give data by age with age roughly correlated with duration of employment as insulation workers. From the data given I estimate SMR for digestive system cancers ~ 300 , 95% confidence limits, 168–495. The comparison population is the male population of Northern Ireland as a whole, which includes a large rural population and so may under-estimate expected cases and thus overestimate the SMR.

Selikoff, Hammond, and Seidman (7) gave doses as proportional to duration of employment. The class intervals are wide, and the groups fews. SMR for digestive cancer: ~ 300 , 95% confidence limits, 215–402. Expected deaths were based on total U.S. white male population, which could lead to an overstatement of SMR.

Newhouse (8) attempted dose-response with crude classification of dose levels (low-moderate exposure vs. severe exposure, and duration of

employment) Men: SMR 152, 95% confidence limits 104–214; Women: SMR 151, 95% confidence limits 75–270.

In the study of Meurman, Kiviluoto, and Hakama (9) no excess of digestive system cancers was found. This study gives per cent of deaths by cause, rather than comparisons to expected. Despite this defect it is safe to say that Finnish anthophyllite miners (as reported in this study) are not at higher risk than the Finnish population as a whole which is already at very high risk for stomach cancer.

General Remarks on Dose-Response

Dose given in terms of years of exposure tends to underestimate risk at high doses. A person has to have not died for a long time in order to be exposed for a long time. Dose given as integrated exposures (exposure \times time) suffer from the same defect.

Using data for instantaneous exposure (i.e., highest level for one week or average level for one month) and separating workers into "continuously exposed," "intermittently exposed," "no longer exposed," much in the manner that smoking and health data are reported might avoid some of the quantitation problems that we have. Enterline reports that maintenance workers show higher response rates for the same exposure than production workers. He speculates that sporadic, high peak exposures may be responsible (in addition to possibly different effects of different forms of asbestos: amosite vs. chrysotile vs. crocidolite, etc.). Reporting dose in terms of peak levels might make the two groups more comparable.

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